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Resveratrol, Pterostilbene, and Piceatannol in *Vaccinium* Berries

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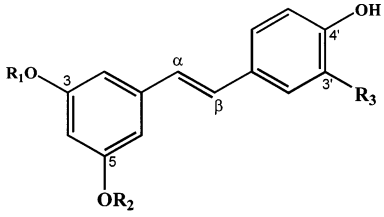
A study was conducted to determine the presence of resveratrol, pterostilbene, and piceatannol in *Vaccinium* berries. Samples representing selections and cultivars of 10 species from Mississippi, North Carolina, Oregon, and Canada were analyzed by gas chromatography/mass spectrometry. Resveratrol was found in *Vaccinium angustifolium* (lowbush blueberry), *Vaccinium arboretum* (sparkleberry), *Vaccinium ashei* (rabbiteye blueberry), *Vaccinium corymbosum* (highbush blueberry), *Vaccinium elliottii* (Elliott's blueberry), *Vaccinium macrocarpon* (cranberry), *Vaccinium myrtillus* (bilberry), *Vaccinium stamineum* (deerberry), *Vaccinium vitis-ideae* var. *vitis-ideae* (lingonberry), and *Vaccinium vitis-ideae* var. *minor* (partridgeberry) at levels between 7 and 5884 ng/g dry sample. Lingonberry was found to have the highest content, 5884 ng/g dry sample, comparable to that found in grapes, 6471 ng/g dry sample. Pterostilbene was found in two cultivars of *V. ashei* and in *V. stamineum* at levels of 99−520 ng/g dry sample. Piceatannol was found in *V. corymbosum* and *V. stamineum* at levels of 138−422 ng/g dry sample. These naturally occurring stilbenes, known to be strong antioxidants and to have cancer chemopreventive activities, will add to the purported health benefits derived from the consumption of these small fruits.

KEYWORDS: ***Vaccinium*; blueberry; cranberry; deerberry; lingonberry; resveratrol; pterostilbene; piceatannol**

INTRODUCTION

Resveratrol, pterostilbene, and piceatannol (**Figure 1**) are naturally occurring compounds belonging to a group called stilbenes, one of the group of phenolics found in grapes and wine. Resveratrol, which is found in considerable quantities in grapes, has been studied the most because its occurrence in wine has been linked to a low incidence of fatal coronary heart disease among populations consuming wine moderately (*1*, *2*). Resveratrol also has been shown to possess cancer chemopreventive activities, demonstrated in in vitro assays representing three stages of carcinogenesis: tumor initiation, promotion, and progression (*3*). The biological and pharmacological activities of resveratrol are thought to be due to its strong antioxidant property, which has been shown in a number of studies: inhibition of Fe^{2+}-induced lipid peroxidation in rat liver microsomes (*4*, *5*); inhibition of Cu^{2+}-catalyzed human (*6*) and porcine (*7*) low-density lipoprotein peroxidation; inhibition of *tert*-butylhydroperoxide-induced lipid peroxidation in human



Resveratrol, $R_1 = R_2 = R_3 = H$, **1**

Pterostilbene, $R_1 = R_2 = CH_3$, $R_3 = H$, **2**

Piceatannol, $R_1 = R_2 = H$, $R_3 = OH$, **3**

Figure 1. Structures of resveratrol (**1**), pterostilbene (**2**), and piceatannol (**3**).

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Table 1. Resveratrol in *Vaccinium* and *Vitis* Samples from Mississippi, North Carolina, and Oregon

scientific name (common name)	cultivar	source	resveratrol[a] (ng/g dry sample)	n^b
V. arboreum Marshall (sparkleberry)	not known	Leakesville, MS	519	2
		Lucedale, MS	125	1
V. ashei Reade (rabbiteye blueberry)	Tifblue	Lamar Co., MS	106	4
		Poplarville, MS	154	3
		Stone Co., MS	61	3
	Climax	Lamar Co., MS	390	4
		Poplarville, MS	77	4
		Stone Co., MS	583	4
	Premier	Lamar Co., MS	7[c]	4
		Poplarville, MS	16[c]	4
		Stone Co., MS	10[c]	3
V. corymbosum L. (highbush blueberry)	Bluecrop	Corvallis, OR	327[d]	2
			853[e]	2
V. elliotti Chapman (Elliot's blueberry)	not known	Poplarville, MS	406	1
		Monticello, MS	453	1
V. stamineum L. (deerberry)	not known	Leakesville, MS	204	2
	B-59	Jackson Springs, NC	331	2
	B-76	Jackson Springs, NC	503	2
	Batesburg White	Jackson Springs, NC	47	2
	NC 78-8-1	Jackson Springs, NC	322	1
	NC 78-8-21	Jackson Springs, NC	104	2
	SHF3A-7:13	Jackson Springs, NC	291	2
	SHF3A-2:14	Jackson Springs, NC	242	2
	SHF3A-2–108	Jackson Springs, NC	115	2
V. vinifera L. (grapes)	Cabernet	Corvallis, OR	2475	2
	Pinot Noir	Corvallis, OR	5746	2
	Merlot	Corvallis, OR	6356	2

[a] Values are means. [b] n = number of replicates. [c] Values are below the limit of quantitation. [d] Sustainable farming. [e] Conventional farming.

fibroblasts (*5*); inhibition of production of reactive oxygen species in porcine platelets (*8*) and in murine macrophages (*9*); direct scavenging of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radicals (*5*, *10*); and inhibition of oxidation of citronellal (*5*).

Using a mouse mammary gland culture assay, pterostilbene was demonstrated to have a cancer chemopreventive activity similar to that of resveratrol (*11*). Pterostilbene is cytotoxic to a number of cancer cell lines in vitro, with the greatest activity against a breast cancer cell line, BC-1 (*12*). It also was shown to have antioxidant (*5*, *11*) and DNA synthesis inhibition (*5*) activities similar to those of resveratrol. Pterostilbene isolated from *Dracaena loureiri* was found to have potent but nonselective activity against cyclooxygenase-1 and cyclooxygenase-2 (*13*). Additionally, pterostilbene was shown to significantly decrease plasma glucose levels with activities comparable to the oral hypoglycemic agent metformin (*14*).

Piceatannol (also known as astringinin) is another resveratrol analogue, which has been demonstrated to inhibit preneoplastic lesions induced by 7,12-dimethylbenz[*a*]anthracene in a mouse mammary organ culture assay (*15*), and is a stronger antioxidant than resveratrol and a potent antiarrhythmic agent (*16*, *17*). Piceatannol isolated from *Rheum undulatum* showed an anti-allergic effect in experimental models of type I allergy, inhibiting 48 h homologous passive cutaneous anaphylaxis in rats and antigen-induced histamine release from rat peritoneal mast cells (*18*). It has also been shown to induce apoptotic cell death in BJAB lymphoma cells with an ED_{50} value equal to resveratrol (25 μM) and also induced apoptosis in an ex vivo assay with leukemic lymphoblast whereas resveratrol did not (*19*). Resveratrol was metabolized to piceatannol by cytochrome P450 enzyme CYP1B1, demonstrating that a natural cancer chemopreventive agent can be converted to an anticancer compound by an enzyme that is overexpressed in a wide variety of human tumors (*20*).

It is apparent from numerous reports and studies that resveratrol, pterostilbene, and piceatannol possess important in vitro and in vivo biological activities, making their presence in grapes and wine of considerable value and generating interest in investigating the presence of these compounds in other berries. Berries from the genus *Vaccinium* are of particular interest because they are one of the most widely consumed small fruits. Additionally, blueberries recently have drawn much attention due to their brain function enhancing activity (*21*, *22*). The objective of this study was to determine the occurrence of resveratrol, pterostilbene, and piceatannol in the fruits of *Vaccinium* species.

MATERIALS AND METHODS

***Vaccinium* and *Vitis* Berries.** *Vaccinium* berries (Family Ericaceae) from Mississippi were collected at various sites (**Table 1**). The samples of rabbiteye blueberry cultivars Climax, Premier, and Tifblue, from Lamar Co., were grown commercially. Those from Poplarville and Stone Co. were harvested from experimental plantings maintained on Ruston fine sandy loam soils (fine, loamy, siliceous, thermic Typic paleudults) by the USDA, ARS, Small Fruit Research Station (SFRS). Samples of sparkleberry, Elliot's blueberry, and deerberry were harvested from wild clones at several Mississippi locations (**Table 1**). Samples (approximately 50 g fresh weight) were randomly collected and placed in chilled containers pending transport to the USDA, ARS, SFRS in Poplarville, MS. The berries were freeze-dried and sent to the Natural Products Utilization Research Unit in Oxford, MS. *Vaccinium* berries from North Carolina were grown at a single location at the North Carolina Agricultural Research Service Experiment Station at Jackson Springs, NC, where supplemental irrigation was applied on as "as-needed" basis. The fruits were collected and shipped overnight to Poplarville, MS, where they were freeze-dried and then sent to Oxford, MS. *Vaccinium* and *Vitis* berries from Oregon were obtained from Stahlbush Island Farms, Corvallis, OR. The berries were grown either by sustainable agriculture methods following farming conditions as certified by the Food Alliance or by conventional farming following current general farming regulations in the Code of Federal Regulations for agriculture. The samples were freeze-dried and then sent to Oxford, MS. The samples from Canada (**Table 2**) were sent as extracts that had been passed through a C18 column. Upon receipt in Oxford, MS,

Table 2. Resveratrol in *Vaccinium* and *Vitis* Samples from Canada

scientific name (common name)	cultivar	source	resveratrol[a] (ng/g dry sample)	n[b]
V. angustifolium Ait. (lowbush blueberry)	not known[c]	Nova Scotia	863	2
V. ashei Reade (rabbiteye blueberry)	Tifblue	United States	1691	3
V. corymbosum L. (highbush blueberry)	not known[c]	Southern United States	1074	3
V. macrocarpon Ait. (cranberry)	not known[c]	Nova Scotia	900	2
V. myrtillus L. (bilberry)	not known[c]	Nova Scotia	768	2
V. vitis-idaea var. *vitis-idaea* (lingonberry)	not known[c]	Nova Scotia	5884	2
V. vitis-ideae var. *minor* (partridgeberry)	not known[c]	Nova Scotia	924	2
V. vinifera L. (grapes)	Table grapes	Nova Scotia	6471	2

[a] Values are means. [b] n = number of replicates. [c] Samples collected in the wild.

all samples were stored (for about 6 months) in a cold room maintained at 4 °C until extraction and analysis.

Extraction of Berries from Mississippi, North Carolina, and Oregon. Berries were extracted using an ASE apparatus (Dionex Corporation, Sunnyvale, CA). One gram of lyophilized berry was mixed with about 10 g of purified sand (Fisher Scientific, Pittsburgh, PA) and loaded in the extraction cartridge. Purified sand was further added in order to pack the extraction cartridge fully. Extraction was carried out with the following parameters: heat, 5 min; static, 10 min; flush volume, 100 mL; purge, 90 s; pressure, 1000 psi; temperature, 40 °C; extraction solvent, methanol:acetone:water:acetic acid (40:40:20:0.1), four cycles. The extract was concentrated under vacuum using a rotary evaporator to remove the organic solvents. The resulting aqueous solution was extracted with 1 mL of ethyl acetate (three times). The combined ethyl acetate extract was evaporated to dryness under a stream of nitrogen.

Extraction of Berries from Canada. Frozen fruit (50 g) was mixed with 3 volumes of methanol:acetone:water:formic acid (40:40:20:0.1), kept for 30 min, and then ground in a Virtis homogenizer (The Virtis Co., Gardner, NY) in a stainless steel flask for 2 min. The extract was filtered through an 11 cm diameter G6 glass fiber filter (Fisher Scientific, Nepean, ON). The residue was extracted a second time with 60 mL of extraction solvent, kept for 30 min, and then ground for 2 min and filtered. The filtrates were combined into a tared round bottom flask, and the organic solvents were removed under vacuum. The remaining aqueous portion was freeze-dried. The freeze-dried extract was suspended in approximately 10 mL of water and loaded on a 10 g C18 column (Waters Scientific, Mississauga, ON), which had been conditioned with 70 mL of methanol and 150 mL of H_2O. The column was washed with 100−150 mL of water. The retained components were eluted with about 50 mL of methanol:acetone:water:formic acid (40:40:20:0.1). The organic components of the solvent were removed under vacuum, and the aqueous portion was freeze-dried.

Analysis of Resveratrol, Pterostilbene, and Piceatannol. The samples were analyzed following a published procedure (*23*) with modifications. One milligram of sample (ethyl acetate extract of berries from Mississippi, North Carolina, and Oregon; C18 column eluate of berries from Canada) was derivatized with 100 μL of a mixture of bis-(trimethylsilyl)trifluoroacetamide:dimethyl formamide:methanol (3.5:1:0.5) in a 2 mL gas chromatography (GC) vial. The vial was capped and heated at 70 °C in a heating block for 1 h. After it was cooled to room temperature, the sample (2 μL injection volume) was analyzed by GC/mass spectrometry (MS) on a JEOL GCMate II system (JEOL USA, Inc., Peabody, MA). The GC temperature program was as follows: initial temperature, 150 °C; increased to 260 °C at a rate of 25 °C/min; then increased to 270 °C at a rate of 1 °C/min; increased to 320 °C at a rate of 60 °C/min; and held at this temperature for 2 min. The GC capillary column used was a 30 m × 0.25 mm i.d., 0.25 μm, ZB-50 (Phenomenex, Torrance, CA). The carrier gas was ultrahigh purity helium (nexAir, Batesville, MS) at a 1 mL/min flow rate. The inlet (splitless), GC interface, and ion chamber temperatures were 250, 250, and 230 °C, respectively.

The analysis of resveratrol, piceatannol, and pterostilbene was carried out using the selected ion monitoring mode (retention times 8.7, 9.5, and 10.2 min, respectively; **Figure 2**). Resveratrol was monitored at *m*/*z* 444 (and 428, 370, and 354 as qualifier ions). Piceatannol was monitored at *m*/*z* 532 (and 516, 443, and 428 as qualifier ions). Pterostilbene was monitored at *m*/*z* 328 (and 312, 296, and 280 as qualifier ions). The qualifier ions were selected as being the most abundant ions in the mass chromatogram of the respective standard samples (**Figure 3**). Quantitation was done using external standards of commercial samples of resveratrol (Sigma-Aldrich, St. Louis, MO) and piceatannol (Calbiochem-Novabiochem Corp., San Diego, CA) and a synthetic sample of pterostilbene (*11*). The limits of detection for resveratrol, piceatannol, and pterostilbene were 1, 21, and 18 ng/g dry sample, respectively. The limits of quantitation for resveratrol, piceatannol, and pterostilbene were 23, 69, and 61 ng/g dry sample, respectively.

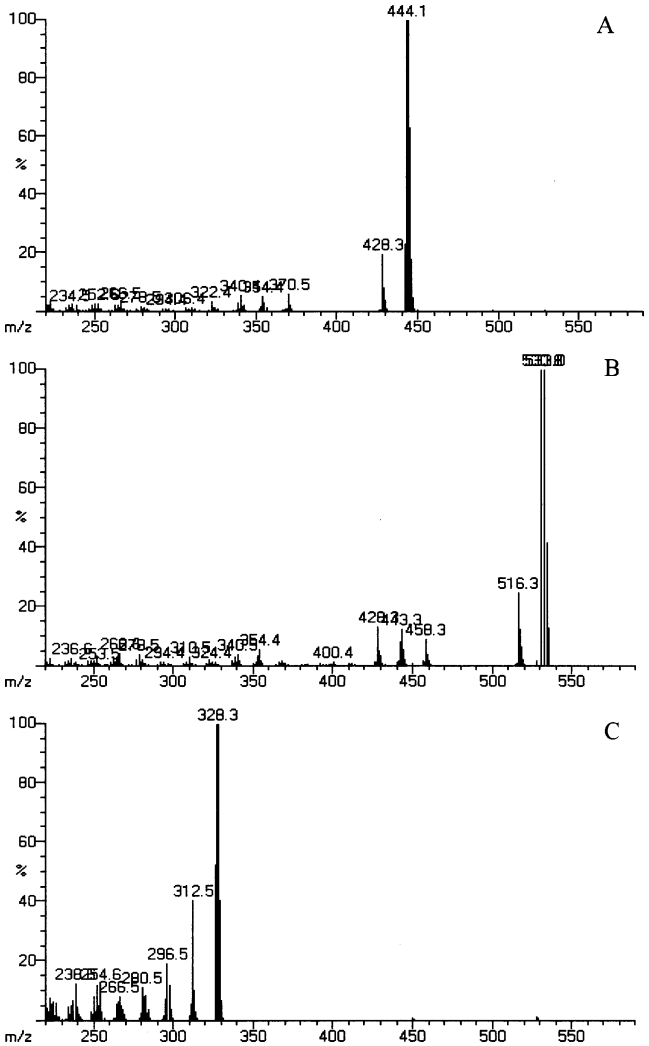

Figure 2. Mass chromatograms of (**A**) resveratrol, (**B**) piceatannol, and (**C**) pterostilbene showing major fragmentations.

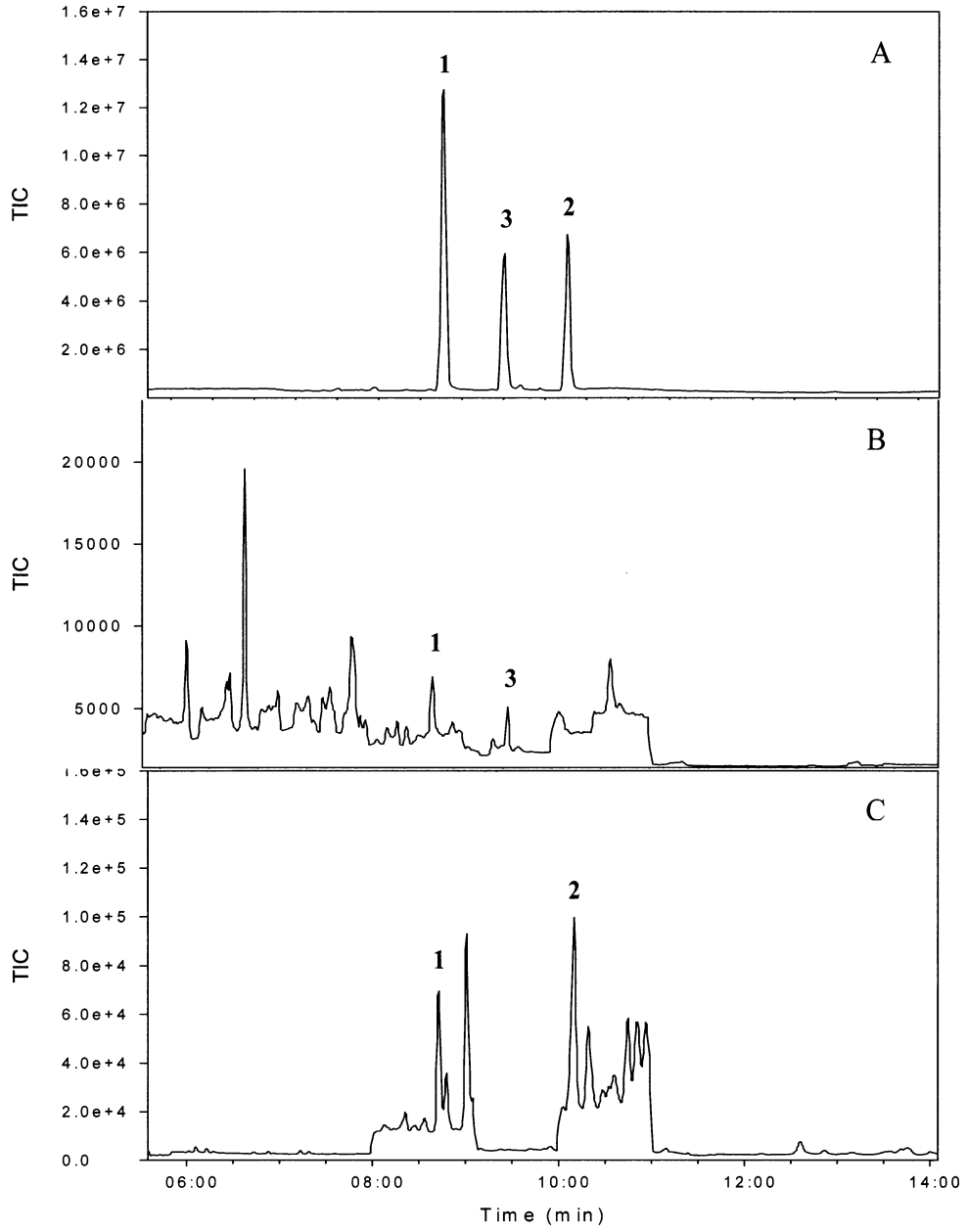

Figure 3. Gas chromatogram of (**A**) a mixture of standard samples of resveratrol (**1**), piceatannol (**3**), and pterostilbene (**2**) with retention times of 8.7, 9.5, and 10.2 min, respectively; (**B**) extract of *V. corymbosum* L. (highbush blueberry) cv. Bluecrop (sustainable) from Corvallis, OR; and (**C**) extract of *V. ashei* Reade (rabbiteye blueberry) cv. Tifblue from Lamar Co., MS.

RESULTS AND DISCUSSION

Vaccinium fruits are known to have a high antioxidant activity. Most studies have correlated their antioxidant activities with total phenolic content (*24*, *25*). It was of interest to determine whether the stilbenes resveratrol, pterostilbene, and piceatannol, which are also reported to have antioxidant activities, are present in *Vaccinium* fruits. Because of the large number of samples, these berries were extracted using an automated extraction apparatus. This apparatus has been found to have a higher extraction efficiency as compared to manual extractions in the extraction of phenolic compounds (*26*). Samples from Canada were received as aliquots of samples from ongoing studies and were preextracted and had been passed through a C18 column. The stilbenes were analyzed by GC/MS using selected ion monitoring. This method allowed for a more selective detection of the stilbenes in the samples.

The amounts of resveratrol, pterostilbene, and piceatannol found in extracts of whole berries of *Vaccinium* species randomly collected from the states of Mississippi, North Carolina, and Oregon and from Canada were variable (**Tables 1**−**3**). Resveratrol was found in all species, and the content varied from 7 to 5800 ng/g dry sample (**Tables 1** and **2**). Higher levels of resveratrol were found in berries from Canada as compared with those from North Carolina, Mississippi, and Oregon. Although a comparative extraction study was not conducted, not being the objective of this study, differences in extraction procedure may account for the higher resveratrol content in samples from Canada. Data on the Canadian samples are included for information purposes. Lingonberry obtained from Canada was found to have the highest content of resveratrol, almost the same as that found in grapes (6500 ng/g dry sample) (**Table 2**). It was not possible to compare the grape

Table 3. Pterostilbene and Piceatannol in *Vaccinium* Samples[a]

scientific name (common name)	cultivar or selection	source	pterostilbene (ng/g dry sample)	piceatannol (ng/g dry sample)
V. ashei Reade (rabbiteye blueberry)	Tifblue	Lamar Co., MS	151[b]	
	Climax	Stone Co., MS	99[b]	
V. stamineum L. (deerberry)	SHF3A-2-108	Jackson Springs, NC	520	
	B-76	Jackson Springs, NC		195
	NC2257	Jackson Springs, NC		138
V. corymbosum L. (highbush blueberry)	Bluecrop[c]	Corvallis, OR		186
	Bluecrop[d]	Corvallis, OR		422

[a] Pterostilbene and piceatannol were not detected in all other samples. [b] $n = 3$; all other samples, $n = 2$. [c] Sustainable. [d] Conventional (see text for details).

resveratrol levels obtained in this study with those reported in the literature because the literature values were based on fresh weights and the analysis was only conducted on grapes skins and not the whole fruit as presented here. Resveratrol has been found in peanuts in concentrations between 30 and 140 ng/g dry sample (*27*). These values are lower than those found in *Vaccinium* berries in this study, except for six samples: *Vaccinium ashei* cv. Tifblue from Stone Co., MS, cv. Climax from Poplarville, MS, and all three samples of cv. Premier, and *Vaccinium stamineum* cv. Batesburg white from North Carolina. The occurrence of resveratrol in *Vaccinium* berries should not be surprising, as its occurrence in the plant kingdom appears to be widespread; for example, it has been reported in *Polygonum cuspidatum* (*28*), *Cassia quinquangulata* (*3*), *Yucca schidigera* (*29*), *Maclura pomifera* (*30*), *Morus* spp. (*31*), *Nothofagus fusca* (*32*), and *Eucalyptus* spp. (*33*). Recently, resveratrol was reported in *Vaccinium angustifolium* from Nova Scotia, Canada, *Vaccinium corymbosum* from Michigan, and *Vaccinium myrtillus* from Poland at levels of approximately 0.0002, 0.0006, and 0.0003 ng/g sample, respectively (*34*). These levels, however, were reported in grams of fresh berries and could not be compared with data in this study, which were analyzed in lyophilized berries.

Resveratrol is synthesized by the action of the enzyme stilbene synthase on *p*-coumaryl-CoA and three malonyl-CoA units, which is encoded by a multigene family (*35*). These genes are induced by biotic and abiotic stresses such as UV light and *Botrytis cinerea* infection (*36*). These stressors probably contributed to the variability of the resveratrol content of the *Vaccinium* berries in the present study especially with the *V. ashei* samples from Mississippi, which showed great variations in the levels of resveratrol. In grapes, the levels of resveratrol were found to vary with the time of harvest, environmental and climatic conditions, and plant developmental stage (*37*−*40*). These factors probably also contributed to the differences in resveratrol levels in *Vaccinium* berries in this study. The stability of resveratrol was demonstrated in a study that showed no change in the content of resveratrol in grapes pomace and skins stored over 5 months in the dark at ambient temperatures varying between 5 and 18 °C (*41*). It is therefore unlikely that storage conditions played a factor in the variation of levels of resveratrol found in this study. The stability of picatannol and pterostilbene on storage is not known and is the subject of future studies.

Pterostilbene was found in only three samples, namely, *V. ashei* cultivars Tifblue from Lamar Co., MS (**Figure 3**), and Climax from Stone Co., MS, and in *V. stamineum* selection SHF3A-2-108 from North Carolina (99−520 ng/g dry sample) (**Table 3**). Piceatannol was found in deerberry, highbush blueberry (**Figure 3**), and blackberry (**Table 3**). In grapes, piceatannol and pterostilbene are generally found in very minute quantities and may be completely absent. Pterostilbene has been detected in fungus-infected grapes at levels of 0.2−4.7 μg/g fresh weight of skin (*42*) and also in healthy grape berries var. Gamay and Pinot Noir at levels of 14−74 ng/g and 120−530 ng/g fresh berries, respectively (*43*). Pterostilbene is the only known stilbene in the genus *Pterocarpus* (*44*) and was found to be one of two antidiabetic compounds isolated from the heartwood of *Pterocarpus marsupium* (*14*). The biosynthesis of pterostilbene is not clearly known. Attempts to synthesize it from resveratrol in a one step reaction using a methyl transferase were unsuccessful (*35*). Piceatannol has been found in significant amounts (0.052 μg/g fresh wt) in *Vitis vinifera* cv. Cabernet Sauvignon (*45*). Like resveratrol, the piceatannol content in grapes is increased by UV-C irradiation (*46*). In a mammalian cell line, piceatannol was synthesized from resveratrol by cytochrome P450 enzyme CYP1B1 (*20*). There is so far no work demonstrating its biosynthesis by a plant P450 enzyme. Piceatannol appears to be present in diverse plant groups: it has been reported in *M. pomifera* (*47*), *Senna skinneri* (*48*), *Rheum* spp. (*18*), and *Cassia* spp. (*49*).

This study has shown that *Vaccinium* berries contain varying amounts of resveratrol, pterostilbene, and piceatannol. It has been hypothesized that additive and synergistic effects of complex mixtures of phytochemicals, instead of a single component, provide the health benefits derived from fruits and vegetables (*50*). The stilbenes in *Vaccinium* berries could add to or act synergistically with other phytochemicals in the berries to produce a more effective complement of protection against coronary heart disease and provide cancer chemoprevention. It is noteworthy that one study indicated that flavonoids are not as active as resveratrol and piceatannol in cancer chemoprevention (*15*). The stilbenes in *Vaccinium* berries may possibly contribute to in vivo physiological effects derived from their consumption such as beneficial effects on brain function (*21*, *22*) and protection against ischemic stroke damage (*51*). Results from this study are encouraging and warrant further studies to determine the content of these stilbenes in *Vaccinium* species and cultivars grown under controlled, identical conditions and select cultivar(s) with high yields of these beneficial compounds.

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